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(54) Title: BLENDS OF GLYCINE DERIVATIVES AND SUGARS (57) Abstract <p>A composition which comprises (a) glycine derivative: $X^1N = C(NX^2Y) - NX^3 - C(X^4X^5) - CO_2H$ where any one or more of X^1, X^2, X^3, X^4 and X^5 is hydrogen or lower alkyl, and Y is hydrogen, lower alkyl, or H_2PO_3 or a substituted variant thereof, or a salt of the derivative, and (b) a sugar in an amount of from about 2 % to about 98 % by weight of the derivative. Preferably, X^3 is methyl, Y is H_2PO_3, and the sugar is a maltohextrin. The sugar is preferably present in an amount of from 40 to 60 % by weight of the glycine derivative.</p>		

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-1-

BLENDS OF GLYCINE DERIVATIVES AND SUGARS

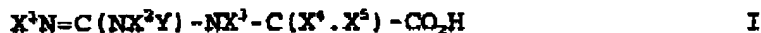
This invention relates to compositions which comprise glycine derivatives and sugars, to pharmaceutical compositions which comprise those compositions and methods of making the compositions.

Creatine exists in muscular tissue of many vertebrates and can be isolated from meat extracts. It has the formula



According to the present invention, it has been found that creatine derivatives blended with one or more sugars can enhance tissue formation in animals.

In one aspect, the invention provides a composition which comprises (a) glycine derivative I



where any one or more of X^1 , X^2 , X^3 , X^4 and X^5 is hydrogen or lower alkyl, and Y is hydrogen, lower alkyl, or H_2PO_3 , or a substituted variant thereof, or a salt of the derivative I, and (b) a sugar in an amount of from about 2% to about 98% by weight of the derivative I.

Preferably, X^3 is methyl.

Preferably, one or more of X^1 , X^2 , X^4 and X^5 is hydrogen.

Preferably, Y is hydrogen, or H_2PO_3 , as will result from a reaction of a glycine derivative with phosphoric acid.

Suitable lower alkyl groups which can be used as substituents in the glycine derivative I are C_1 to C_4 , straight or branched, groups.

-2-

The glycine derivative I may be present in a hydrated form, for example as the monohydrate.

The glycine derivative may be present as a salt, for example as the sodium or potassium salt.

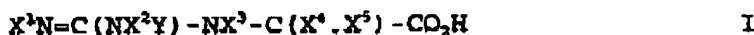
The sugar may be selected from a group consisting of dextrose, fructose, glucose and maltose. It is preferred that the sugar is a maltodextrin. Maltodextrins comprise polymers of glucose, and will generally have a dextrose equivalent which is less than about 20, as determined by the Lane-Eynon titration technique (see Pearson's Chemical Analysis of Foods). Maltodextrins can be derived from corn or maize. They often include small amounts of potassium, sodium, and sulphur dioxide.

Preferably, the amount of sugar present in the composition is at least about 30%, more preferably at least about 40%, by weight of the glycine derivative.

Preferably, the amount of sugar present in the composition is not more than about 70%, more preferably not more than about 60%, by weight of the glycine derivative.

In another aspect, the invention provides a pharmaceutical composition which comprises a composition of the type referred to above, in association with a solid or liquid a pharmaceutical carrier or diluent.

In a further aspect, the invention provides a method of making a pharmaceutical composition which comprises mixing (a) glycine derivative I



where any one or more of X^1 , X^2 , X^3 , X^4 and X^5 is hydrogen or lower alkyl, and Y is hydrogen, lower alkyl, or H_2PO_4 or a

-3-

substituted variant thereof, or a salt of the derivative I, and
(b) a sugar in an amount of from about 2% to about 98% by
weight of the derivative I.

The composition of the present invention can be used as a
metabolic supplement. It can be used to enhance tissue
formation, for example in the treatment of diseases, especially
wasting diseases such as multiple sclerosis. It has been found
that the composition is particularly well suited to enhancing
cardiac tissue formation. It can also be used to prevent
disease. It has the advantage that its principal constituents
are occur naturally. Furthermore, the composition has a
pleasant taste, and is stable under normal conditions.

The composition has been found to be suitable for use in the
treatment of:

- mood disorders, such as bipolar, depressive disorders;
recurrent depression disorders; schizo-affective dis-
orders; dysthymia;
- schizophrenia
- dementias, such as Alzheimer's disease; neurotic
illness including phobic anxiety disorders; obsessive
compulsive disorders; reaction to severe stress; neur-
asthenia, general anxiety states;
- chronic fatigue syndrome, including myalgia encephalo-
myeletis (ME).

In another aspect, the invention provides the use of a
composition of the type discussed above in the manufacture of
a medicament, especially for the treatment of one or more of
the conditions referred to above.

-4-

The composition of the invention can be administered in tablet form. It can be administered in powder form. It can be preferred for the composition to be administered in solution, in particular in aqueous solution; it can be particularly preferred to administer the composition in solution, possibly at elevated temperature, which might be the highest temperature at which the solution can comfortably be consumed. For example, the solution might be heated to a temperature which is greater than about 40°C, preferably greater than about 50°C, for example greater than about 60°C, or even higher. Administering the composition in this way has been found to facilitate absorption.

It can be preferred for the temperature of solution to be less than about 55°C when administered, more preferably less than about 45°C, even less than 40°C. This feature allows breakdown of the glycine derivative to be minimised. When the composition is dissolved in solution at a temperature which is elevated to facilitate dissolution, the temperature is preferably then lowered by addition of a liquid at lower temperature (which might be flavoured) to reduce the overall temperature of the solution.

When administered in solution, it can be preferred for the effective concentration of the glycine derivative to be greater than about 0.5% by weight, more preferably greater than about 0.7%, especially greater than about 1.0%. The concentration can be less than about 15% by weight, preferably less than about 10%, more preferably less than about 5%. Suitable concentrations are from about 1.5% to about 5%.

The invention will now be described with reference to certain examples.

EXAMPLE 1

-5-

Tablets were formed from a mixtur of creatine monohydrate supplied by Chemielinz A G, and a maltodextrin supplied by Roquette Frères S A under the trade name Glucidex 19, in a ratio by weight 2:1, the two constituents being provided in powder form. Tablets were formed using conventional tablet presses from the resulting mixture.

EXAMPLE 2

Tablets were formed from a mixture of the creatine monohydrate used in Example 1 and a glucose polymer supplied by Edward Mendell & Co under the trade name Emdex, in a ratio by weight 2:1, the two constituents being provided in powder form. Tablets were formed using conventional tablet presses from the resulting mixture.

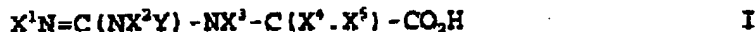
EXAMPLE 3

Tablets were formed from a mixture of the creatine monohydrate used in Example 1 and a dextrose polymer supplied by Cerestar Limited under the trade name Celellose, in a ratio by weight 2:1, the two constituents being provided in powder form. The mixture of the powders was supplied for ingestion in powder form.

-6-

CLAIMS:

1. A composition which comprises (a) glycine derivative I



where any one or more of X^1 , X^2 , X^3 , X^4 and X^5 is hydrogen or lower alkyl, and Y is hydrogen, lower alkyl, or H_2PO_4 , or a substituted variant thereof, or a salt of the derivative I, and (b) a sugar in an amount of from about 2% to about 98% by weight of the derivative I.

2. A composition as claimed in claim 1. in which X^3 is methyl.

3. A composition as claimed in claim 1 or claim 2, in which Y is H_2PO_4 .

4. A composition as claimed in any one of claims 1 to 3, in which the sugar is selected from a group consisting of dextrose fructose, glucose and maltose.

5. A composition as claimed in claim 4, in which the sugar is a maltodextrin.

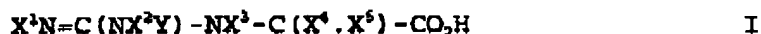
6. A composition as claimed in any one of claims 1 to 5, in which the sugar is present in an amount of from about 30% to about 70% by weight of the glycine derivative.

7. A composition as claimed in claim 6, in which the sugar is present in an amount of from about 40% to about 60% by weight of the glycine derivative.

8. A pharmaceutical composition which comprises a composition as claimed in any one of claims 1 to 7 in association with a solid or liquid carrier or diluent.

-7-

9. A method of making a pharmaceutical composition which comprises mixing (a) glycine derivative I



where any one or more of X^1 , X^2 , X^3 , X^4 and X^5 is hydrogen or lower alkyl, and Y is hydrogen, lower alkyl, or H_2PO_4 , or a substituted variant thereof, or a salt of the derivative I, and (b) a sugar in an amount of from about 2% to about 98% by weight of the derivative I.

10. A method as claimed in claim 9, in which the glycine derivative I and the sugar are mixed in powder form.

11. Use of a composition as claimed in any one of claims 1 to 7 in the manufacture of a medicament.

INTERNATIONAL SEARCH REPORT

Internat'l Application No
PCT/GB 94/00181

A. CLASSIFICATION OF SUBJECT MATTER IPC 5 A61K31/195		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols) IPC 5 A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 339 814 (UNITIKA LTD) 2 November 1989	1-4,6-9
Y	see page 4, line 39 - page 5, line 2	5
X	EP,A,0 370 994 (LUBEC, GERT, PROF. DR.) 30 May 1990	1,2,4,8,9,11
Y	see column 7, line 20 - line 52	5
X	GB,A,1 208 398 (CALBIOCHEM) 14 October 1970 see examples 1-3	1-4,8-10
<input type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
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Date of the actual completion of the international search 2 May 1994		Date of mailing of the international search report 18.05.94
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INTERNATIONAL SEARCH REPORT

Information on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0339814	02-11-89	JP-A- 1257266	13-10-89
		DE-D- 68909995	25-11-93
		DE-T- 68909995	10-02-94
EP-A-0370994	30-05-90	AT-B- 393079	12-08-91
		AT-B- 393080	12-08-91
		JP-A- 2145514	05-06-90
		US-A- 5077313	31-12-91
GB-A-1208398	14-10-70	BE-A- 700778	02-01-68
		CH-A- 514841	31-10-71
		DE-A- 1598321	24-02-72
		DE-B- 1598325	11-01-73
		DE-A- 1598326	02-03-72
		FR-A- 1527437	
		FR-A- 1527438	
		GB-A- 1163409	04-09-69
		GB-A- 1191697	13-05-70
		GB-A- 1192046	13-05-70
		NL-A- 6708570	02-01-68
		US-A- 3413198	
		US-A- 3527331	08-09-70
		US-A- 3527332	08-09-70
		US-A- 3527674	08-09-70
		US-A- 3539460	10-11-70
		US-A- 3539453	10-11-70
		US-A- 3540984	17-11-70

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